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Modulation of Human Medial Temporal Lobe Activity by Form, Meaning, and Experience

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ABSTRACT: Clinically, the hallmark of the human amnesic syndrome is an impaired ability to consciously recollect or remember daily events. If the medial region of the temporal lobes, including the hippocampus and related structures, is critical for establishing these new memories, then this brain region should be active whenever events are experienced, regardless of whether subjects are asked explicitly to learn and remember. Here we show that the medial temporal region is active during encoding and that the hemisphere activated and the amount of activation depend on the type of stimulus presented (objects or words), whether the stimulus can be encoded for meaning (real objects and words versus nonsense objects and words), and task experience (first versus the second time a task is performed). These findings demonstrate that the medial temporal lobe memory system is engaged automatically when we attend to a perceptual event and that the location and amount of activation depend on stimulus characteristics (physical form, meaning) and experience. *Hippocampus 1997;7:587–593.*

KEY WORDS: positron emission tomography; PET; memory; cognition; hippocampus; encoding

A major functional characteristic of the medial region of the human temporal lobes is material-specificity (Milner, 1972). Left-sided lesions impair explicit memory for verbal material while right-sided lesions impair explicit memory for nonverbal material. A major functional characteristic of human memory is encoding-sensitivity (Craik and Lockhart, 1972). Material encoded for meaning is better remembered than material encoded for perceptual features. Yet, to date, no functional brain imaging study has shown that the side and amount of medial temporal lobe activity is modulated by the type of material presented and the processing demands of the encoding task. In fact, functional brain imaging studies have often failed to find memory-related activation of this region, even under conditions when such activations would be expected (for exceptions, see Haxby et al., 1996; Schacter et al., 1996; Stern et al., 1996; Gabrieli et al., 1997; and for recent reviews, see Cabeza and Nyberg, 1997; Fletcher et al., 1997; Tulving and Markowitsch, 1997). One explanation for why medial temporal activation is not always found is that this region may be continuously active (Fletcher et al., 1995), and this may be especially so during a dramatic and novel event such as a brain scan. As a result, medial temporal activity cannot be detected easily because this region is also active during the baseline task against which the memory tasks are contrasted. This idea is consistent with studies of patients with medial temporal lesions (Knight, 1996) and with functional brain imaging studies of normal subjects (Tulving et al., 1994; 1996) that suggest that the hippocampus is preferentially involved in novelty detection. We reasoned that a baseline task that captures the subject's attention, yet contains no specific stimulus information, might produce minimal medial temporal lobe activity and thus provide a background against which activation of this region could be detected.

To accomplish this goal, subjects stared at briefly presented visual noise patterns. This baseline task was compared with scans during which subjects silently encoded different types of material presented for the same duration, and at the same rate, as the visual noise patterns. During these encoding scans subjects stared at nonsense objects, silently named real objects, silently read pronounceable nonsense words, and silently read real words. They were not instructed to learn the material, nor was memory tested at any time during the experiment. There were two scans for each of these conditions, but with different, not previously seen, items during each scan.

Using statistical parametric mapping (SPM), we compared rCBF data from all of the encoding conditions combined (eight scans) with the activity measured during the visual noise baseline scans (two scans). This analysis revealed strong, bilateral activation of the medial temporal lobes and of the ventral occipitotemporal region with maximal activity in the occipital lobes (fusiform gyrus) (Fig. 1). To determine how these activations were modulated during the experiment, separate hemisphere (left, right) by stimulus (noise patterns, nonsense objects, nonsense words, real objects, real words) analyses of variance (ANOVAs) were performed for the medial temporal and ventral occipital regions. The data for these analyses were the rCBF values measured at the pixels of peak activity identified by the SPM analysis.

Analysis of the medial temporal lobe activity revealed a main effect of stimulus ($F(4, 60) = 10.2$; $P < .0001$) which varied as a function of hemisphere (hemisphere by stimulus; $F(4, 60) = 7.3$; $P < .0001$) (Fig. 2A). Planned

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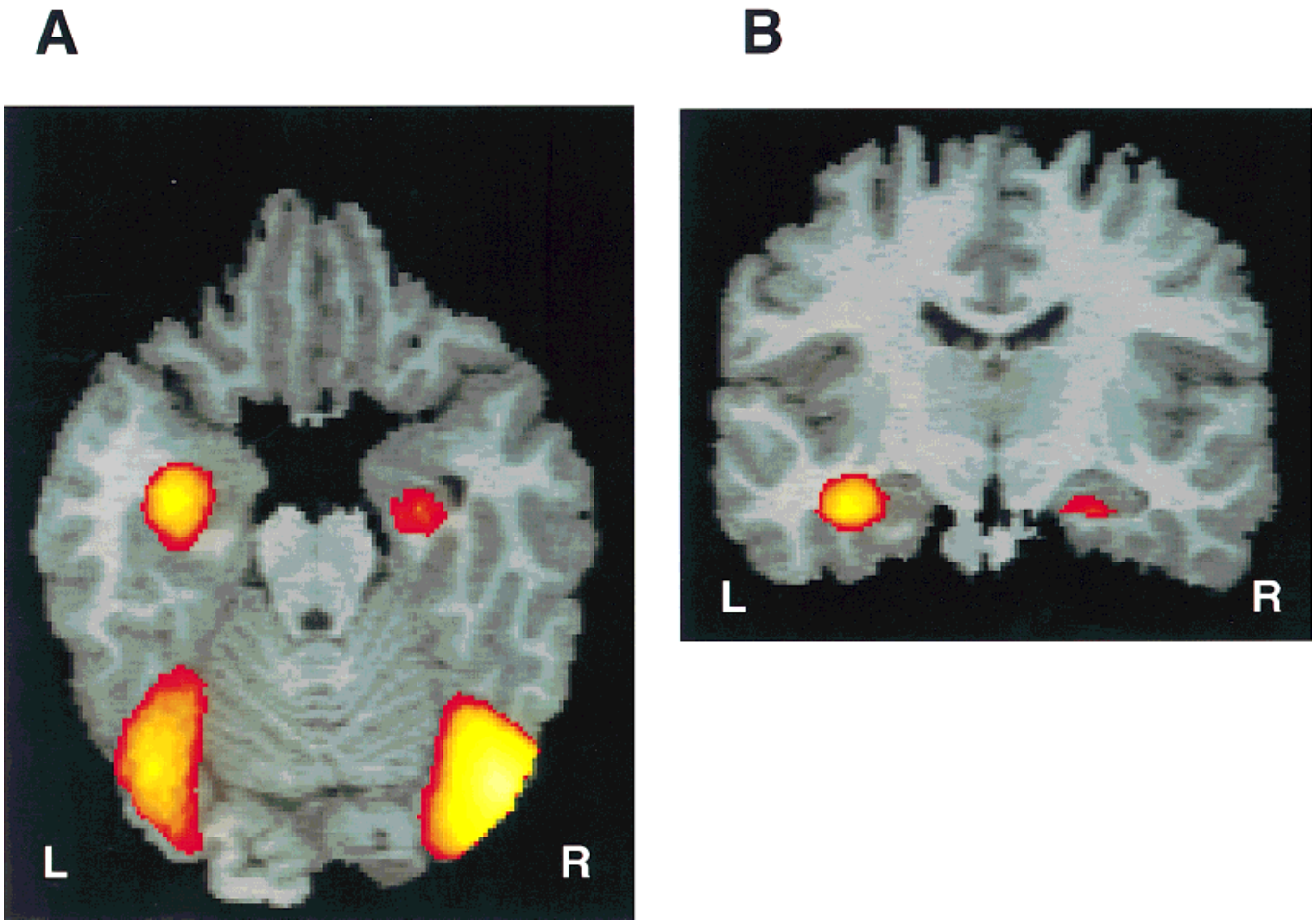


FIGURE 1. Pixels that exceeded a threshold of Z = 3.09, $P < .001$ when all stimulus encoding conditions were compared to the visual noise baseline condition. A: Horizontal section, 20 mm below the anterior–posterior commisural line where medial temporal lobe activity was maximal. Peak activations, expressed in millimeters as coordinates in the Talairach and Tournoux brain atlas (Talairach and Tournoux, 1988), were at −34, −16, −20 (Z score = 4.63), and +22, −18, −20 (Z = 3.74) in the left and right medial temporal region, respectively. Also shown are activations in the fusiform gyrus with maxima at −40, −74, −8 (Z > 7.98) in the left, and +40, −70, −16 (Z = 6.50) and +30, −88, +4 (Z = 5.78) in the right occipital lobes (BA 18). The only other activation was in the left precentral gyrus (BA 4) (−28, −2, +24; Z = 3.43) (not shown). B: Coronal section through the medial temporal region, 17 mm posterior to the anterior commissure.

comparisons indicated that, relative to the activation associated with staring at the visual noise patterns, the left medial temporal lobe responded to all types of material (all P's $< .05$). Moreover, the amount of left medial temporal lobe activation varied markedly as a function of meaning (greater activity for real objects and words than for nonsense objects and words; $F(1, 60) = 27.4$, $P < .0001$), but not as a function of physical form (no difference between objects and words; $F < 1.0$). In contrast, the right medial temporal region responded strongly to objects (real and nonsense), and thus activity in this area was modulated by stimulus form (greater for objects than words; $F(1, 60) = 27.8$, $P < .0001$) but not by meaning (no difference between meaningful words and objects relative to nonsense words and objects; $F < 1.0$).

Because overall activity in the left medial temporal region tended to be greater on the left than on the right (main effect of hemisphere $F(1, 15) = 3.9$, $P = .07$), the rCBF from each encoding condition was converted to percent change scores relative to the visual noise baseline, again using the data from the pixels of peak activity identified by SPM. A hemisphere (left, right) by form (object, word) by meaning (meaningful, meaningless) ANOVA revealed significant interactions between hemisphere and form ($F(1, 15) = 5.8$, $P < .05$) and hemisphere by meaning ($F(1, 15) = 13.0$, $P < .001$). Consistent with the analysis of the normalized rCBF data, activity in the left medial temporal region was modulated by meaning ($F(1, 15) = 12.7$, $P < .005$) but not by form, whereas activity in the right medial temporal region was modulated by stimulus form ($F(1, 15) = 26.2$, $P < .0001$) but not be meaning (Fig. 2B).

To identify the location of the material-specific activations, separate SPM comparisons of each stimulus encoding condition with the visual noise baseline scans were performed (e.g., both silent object naming scans compared to both visual noise pattern scans). As illustrated in Figure 3, there was bilateral activation of the medial temporal region for objects that was stronger on the

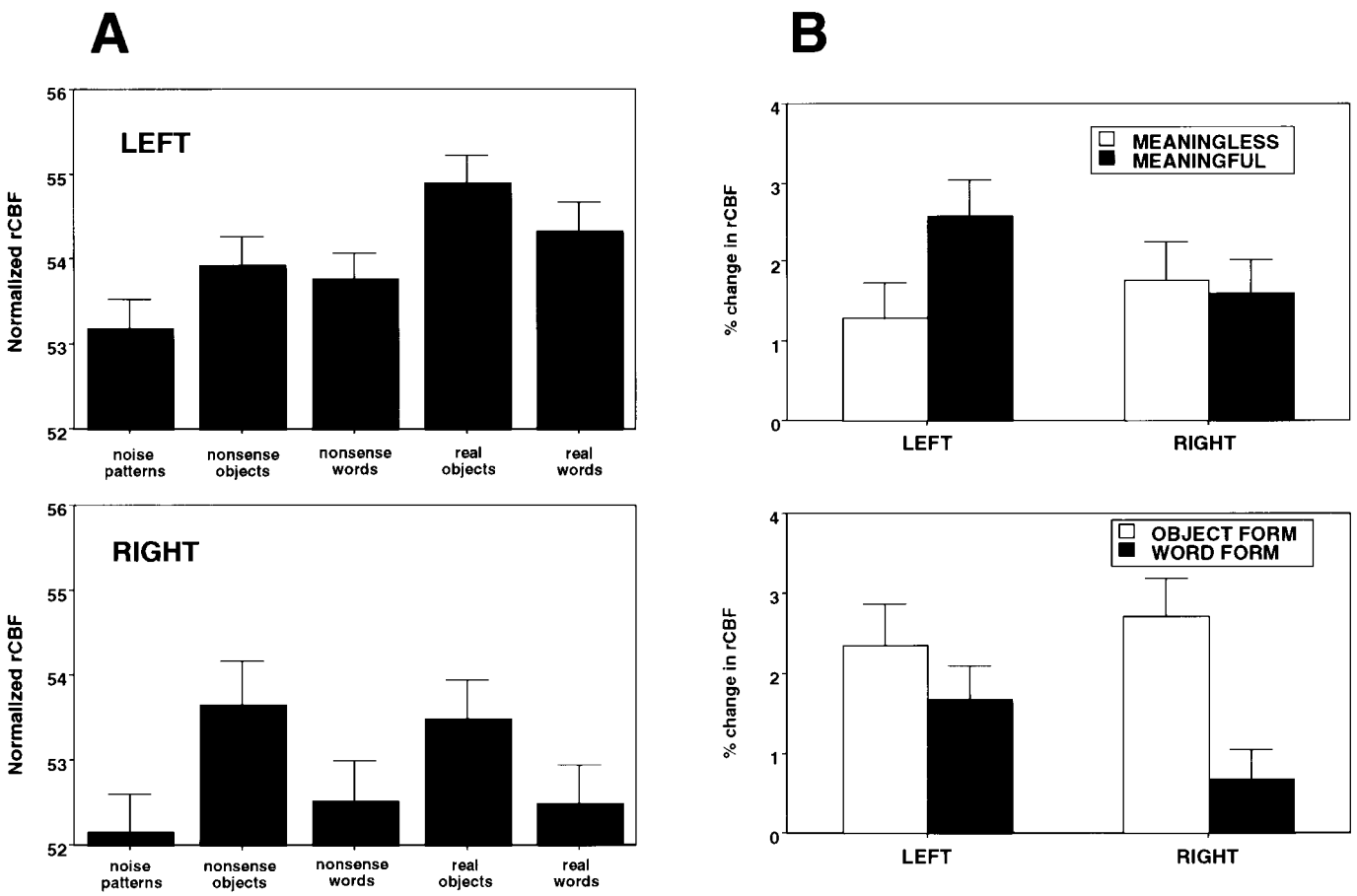


FIGURE 2. A: Normalized rCBF data at the site of peak activity in the left and right medial temporal regions shown in Figure 1. B: Percent increase in normalized rCBF, relative to the visual noise pattern baseline, for meaningless and meaningful material (collapsed across objects and words; upper panel), and for object forms and word forms (collapsed across meaningless and meaningful material; lower panel).

left for real than for nonsense objects, whereas words produced left-sided activity, stronger for real than nonsense material (see Note). In addition, the word-related activations were located approximately 1 cm anterior to the object-related activations (Fig. 3).

In contrast, and consistent with their role in the early stages of visual processing, analysis of activity in the ventral occipital lobes revealed only a main effect of stimulus ($F(4, 60) = 29.6$, $P < .0001$). Collapsed across hemispheres, planned comparisons indicated increased rCBF when encoding each type of material relative to the visual noise baseline (all P's $< .0001$). This activity varied as a function of the physical form (greater for objects than words; $F(1, 60) = 24.5$, $P < .0001$), but not as a function of meaning (no difference between meaningful words and objects relative to nonsense words and objects; $F < 1.0$). This latter finding is consistent with previous functional brain imaging data showing comparable activation of occipital cortex for meaningful and meaningless objects (Malach et al., 1995; Martin et al., 1996).

The pattern of left and right medial temporal lobe activations provide a basis for understanding the material-specific memory deficits observed in patients who have undergone unilateral resection of the anterior temporal lobe, including the medial structures, for relief of intractable epilepsy (e.g., Milner, 1972). Our findings suggest that the explicit memory deficit in these patients is due, at least in part, to disrupted processing at initial encoding. In addition, the increased activation of the left medial temporal region for meaningful relative to meaningless material indicates that activity in this region is sensitive to encoding processes that determine, in part, the likelihood that an event will be remembered. Material encoded for meaning is better remembered than material encoded along physical dimensions (Craik and Lockhart, 1972). This levels-of-processing memory effect for the material used in the present study was verified in an independent group of subjects ($n = 12$) who showed better incidental memory for real objects than nonsense objects (mean recognition accuracy = 89.9% and 71.5%, respectively; $t(11) = 13.8$, $P < .0001$) and for real words than nonsense words (76.6% and 65.3%, respectively; $t(11) = 5.3$, $P < .001$). Performance in all conditions was significantly better than chance (all P's $< .001$).

However, our finding of left, but not right, medial temporal activation when reading nonsense words appears to run counter to claims that the right medial temporal lobe is part of a novelty detection network (Tulving et al., 1994, 1996). Novelty, however,

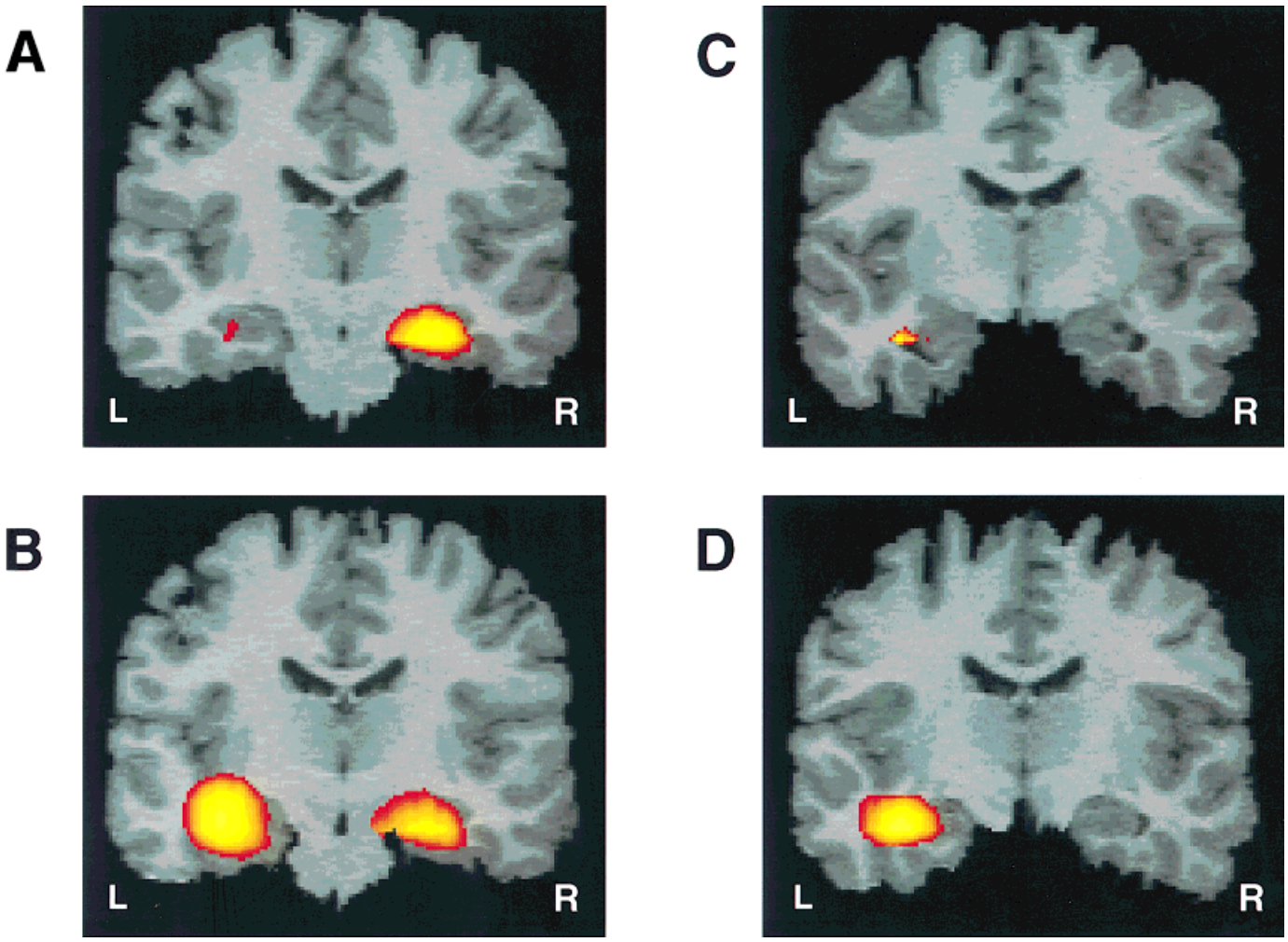
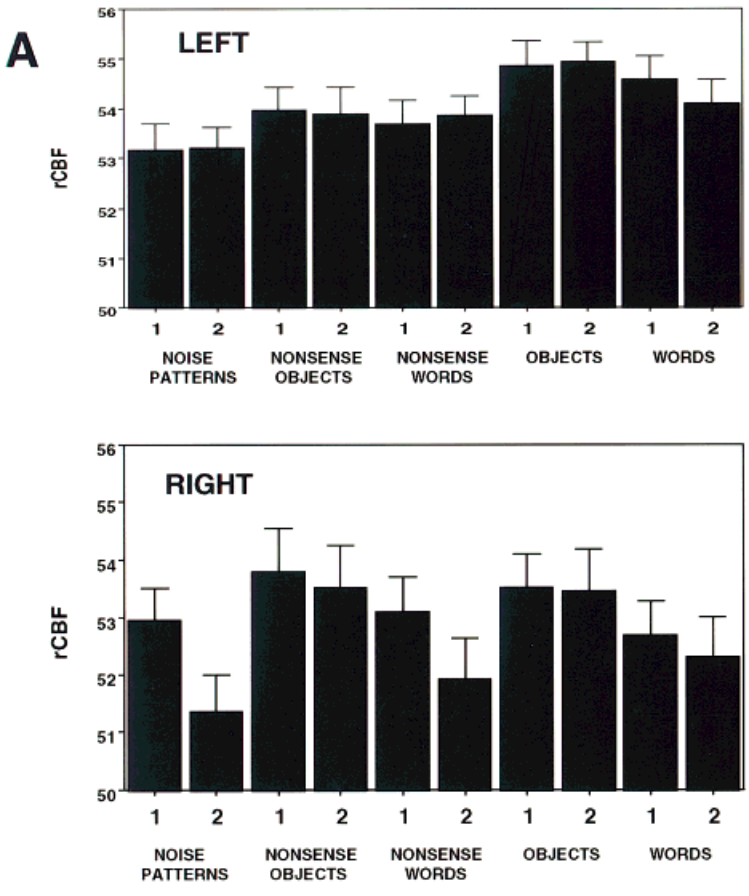


FIGURE 3. above.



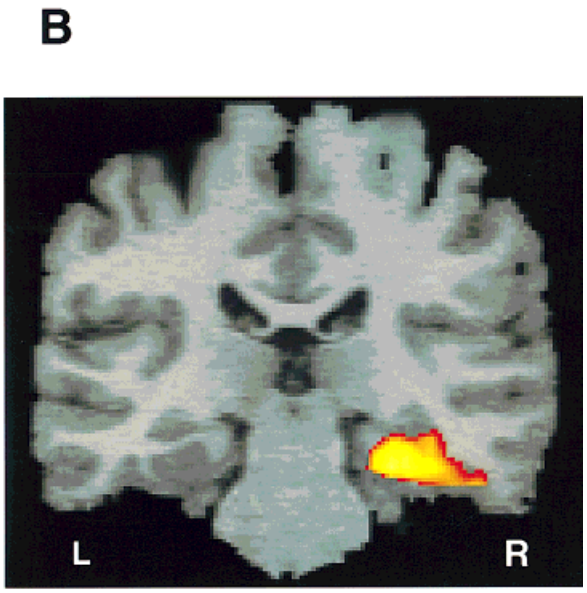


FIGURE 4.

can be defined in several ways. First, novelty can be defined in terms of an item's inherent meaning. In this sense, nonsense words are more novel than real words. Second, as intended by Tulving, novelty can be defined with regard to recent experience with a particular item. Thus, in the context of a memory experiment, items not previously presented are more novel than items that were studied. Third, novelty can be defined by task experience. The first time a task is performed is more novel than the second time.

Since our study included two PET scans for each type of material, with different stimuli presented on each scan, we could directly evaluate the effect of task experience on the pattern of rCBF, independent of the effects of stimulus repetition. To examine novelty in this sense, the medial temporal and occipital rCBF values were submitted to additional ANOVAs with scan order included as a factor. Within the medial temporal region there was a significant interaction between side of activity and experience (hemisphere by scan order $F(1, 15) = 5.4$, $P < .05$; the three-way interaction of hemisphere by stimulus by scan order was not significant, $F = 1.7$). Specifically, whereas activation of the left medial temporal region remained constant across the first and second scans of each stimulus type (thus, during the second half of the experiment relative to the first half; $F < 1.0$), the right medial temporal region showed decreased activity on the second scans relative to the first scans ($F(1, 15) = 12.7$, $P < .005$) (Fig. 4). Again, the posterior, ventral region of the occipital lobes showed a different pattern of response: a decrease in activity with task repetition (scan order, $F(1, 15) = 7.0$, $P < .05$) that was of equal magnitude in the right and left hemispheres (hemisphere by scan order, $F < 1.0$).

Because different items were shown during each scan, this decreased activity does not reflect perceptual priming, but rather must be related to a more general orienting or habituation response. Our finding for the medial temporal region is consistent with studies showing a greatly reduced orienting response in humans with unilateral damage to the hippocampus (Knight, 1996), especially following right-sided damage (Davidson et al., 1992). This finding also explains why incidental recall may be worse following right than left hemisphere lesions, even for verbal material (Luria and Simernitskaya, 1977).

The medial temporal region (including the hippocampus proper, parahippocampal, perirhinal, and entorhinal cortices) plays a critical role in establishing new episodic or declarative memories (Squire, 1992). To support this learning this region must be active when events are experienced. Our findings show that, in the normal human brain, the medial temporal region is automatically engaged during stimulus encoding (cf. Moscovitch, 1995) and that the hemisphere maximally engaged depends on the type of material presented. Material that requires graphemic (words), phonetic (words and real objects), and lexical and semantic processes (real words and real objects) produced greater left-, than right-sided activation, whereas right-sided activity was modulated by stimulus form (greater for objects than for words). Moreover, activity in the left medial temporal region increased for meaningful relative to meaningless material, suggesting a dominant role in mediating level of processing effects (Kapur et al., 1994), whereas activity in the right medial temporal region decreased with task experience, suggesting a dominant role in novelty detection (Tulving et al., 1996). These findings demonstrate that the medial temporal lobe is continuously active and thus provide an explanation for why it has been difficult to observe activity in this region when different tasks are directly contrasted (Haxby, 1996). Nevertheless, the *amount* of medial temporal lobe activity is not constant, but rather is enhanced by meaningfulness and novelty, which in turn result in better remembering.

FIGURE 3. Location of activations in the medial temporal region when subjects (A) stared at nonsense objects (left = −30, −22, −16; Z = 2.36, right = +26, −18, −20; Z = 4.57), (B) named real objects (left = −34, −20, −16; Z = 5.40; right = +24, −24, −20; Z = 4.97), (C) read nonsense words (left = −34, −12, −20; Z = 2.78), and (D) read real words (left = −33, −15, −20; Z = 4.52). Shown are all pixels that exceeded a threshold of Z = 2.32, $P < .01$ compared to the rCBF values obtained during the visual noise baseline condition. Additional activations (not shown) in the left precentral gyrus (BA 4) when silently reading nonsense words (−30, −8, +24, Z = 3.35) and in the left inferior frontal/insula region (Broca's area) when silently reading real words (−40, +10, +4, Z = 3.15) and silently naming objects (−38, +19, +4, Z = 4.05) suggest that the subjects engaged in the encoding tasks (reading and naming).

FIGURE 4. A: Normalized rCBF values in the left (upper panel) and the right (lower panel) medial temporal sites identified in Figure 1 during the first and second scan for each type of material presented. B: Location of activation in the right medial temporal region (maximum at +36, −16, −24; Z = 4.29) for the first scans of each condition relative to the second scans. There was also a more posterior activation in the region of the right parahippocampal gyrus (+24, −32, −20; Z = 4.70, not shown). Additional activations (not shown; Z > 3.09) were bilaterally in the cerebellum and posterior temporoparietal cortex (BA 22, 40), the right temporal lobe, extending anteriorally along the middle and inferior temporal gyri (BA 21, 20) from approximately 5 cm to 1 cm posterior to the anterior commisural line, the left amygdala, the left temporal pole (BA 38), and the right inferior frontal cortex (BA 45, 47).

DETAILED METHODS

The study included 16 right-handed individuals (equal number of males and females; age range 20–40 years) who gave their informed consent. During scanning, each stimulus was presented for 500 ms, followed by a centrally located fixation cross for 1,500 ms. Fifty different items were shown during each scan. Stimuli consisted of visual noise patterns (Martin et al., 1996), line drawings of common objects (most from Snodgrass and Vanderwart, 1980), line drawings of nonsense objects (Kroll and Potter, 1984), English words (concrete nouns), and pronounceable nonsense words (Wiggs and Martin, 1994). All words contained two to three syllables and were five to eight letters in length. The English words were drawn from 12 different semantic categories, and lists used for each scan were equated for word frequency

(Kucera and Francis, 1967) and category membership. Objects were drawn from 15 different semantic categories, and lists used for each scan were equated for name frequency (Kucera and Francis, 1967), category membership, and category typicality (Battig and Montague, 1969). The order of conditions was counterbalanced across subjects except that the visual noise baseline conditions were always the first and last scans.

PET scans were obtained using a Scanditronix PC2048-15B tomograph (Milwaukee, WI) which acquires 15 continuous, 6.5-mm-thick cross-sectional images. Within-plane resolution is 6.5 mm (full width at half maximum). Subjects began the task approximately 30 s prior to injection of 30.0 mCi of $H_2{}^{15}O$. Data from each subject were normalized to his/her own global mean flow (ratio correction). Contrasts between tasks were evaluated with t-tests, and then converted to z scores using statistical parametric mapping (SPM) (Friston et al., 1990, 1991a,b). Activations are displayed on a high-resolution MRI from a single subject stereotactically transformed to the Talairach and Tournoux (1988) templates.

Additional analyses (ANOVAs) were computed on the rCBF values from the sites of peak activity identified by the SPM comparison of all the encoding condition scans to the visual noise pattern baseline scans.

Unless otherwise noted, only the findings for the medial temporal region are reported here. Separate comparisons of each stimulus type relative to the visual noise baseline revealed several stimulus-specific activations that did not reach threshold when all of the encoding conditions were combined and contrasted with the visual noise pattern baseline. These stimulus-specific activations, which included the ventral temporal lobes for real objects and the left superior temporal gyrus for words, will be reported elsewhere.

Twelve subjects (age range = 23–38 years) who had not participated in the PET study provided behavioral data for the incidental memory study. Subjects were told that we were piloting a procedure for a brain imaging study for which we needed to ensure the material would be visible. The same stimuli were presented under the same viewing conditions as used in the PET study. Subjects were instructed to stare at the nonsense objects, and to silently name the objects and read the words. Subjects viewed items of each type with list order counterbalanced across subjects. Following the last list, subjects were given a surprise, forced-choice recognition memory test. For each subject, the order of the memory tests was the same as the order used during the encoding period.

NOTE

The strong activation of the right medial temporal region associated with attending to nonsense objects replicates our previous finding (Martin et al., 1996). In that report we noted that the hippocampus was not active when subjects silently named objects. Although this was true with regard to the location of the hippocampus as defined by the Talairach and Tournoux brain atlas, there was activity medial and superior to the hippocampus, extending into the left pulvinar. The location of the peak of that activation, −14, −28, −4, is close to other reports of medial temporal lobe activation (e.g., −20, −28, −8 for word recognition memory compared to passive fixation; Schacter et al., 1996). Thus, there may have been medial temporal lobe activation associated with object naming in our previous report, albeit on the left rather than bilaterally as found in the present study. The reason for these differences remains to be determined.

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